Appendices 1 and 2

As required by 37 CFR 1.121(e)(j) enclosed herewith as Appendix 1 is a clean set of all the claims now pending. Also enclosed herewith as Appendix 2 is a marked up version of the changes made to the claims to indicate how the previous version of the claims have been modified to produce the clean replacement paragraphs. The modifications are indicated by underlining and in bold type for additions, and by strikeouts for deletions.

REMARKS

Claim 31 has been cancelled and Claims 24, 25 and 32 have been amended to point out with more particularity and clarity the subject matter regarded by the Applicant as his invention. Claim 24 has been merged with the cancelled Claim 31 to point out that the type of germline mutations detected by the subject invention are truncating-causing mutations and mutations that cause allelic loss.

Claim 25 has been amended to correct proofreading/ grammatical errors that the Examiner noted. Claim 32 has been amended to correct its dependency on a cancelled claim.

Applicant respectfully concludes that no new matter has been entered by the above claim amendments.

Election/Restriction

The Office Action mistakenly states on page 2 that: "Applicant traversed the election of species requirement on the

basis that the species are presented in claims reciting species are Markush claims and that the courts have stated that in many cases Markush claims do not include inventions that would otherwise be considered independent." [Emphasis added.] Applicant respectfully points out that quite to the opposite, the response to the second Restriction Requirement submitted to the PTO on August 15, 2001 reports that:

> a series of decisions from the Court of Customs and Patent Appeals (CCPA) . . . culminating in In re Harnisch, id., specifically states that in many cases Markush claims do include inventions which would otherwise be considered independent and distinct [MPEP Section 803.02]. Thus, Applicant respectfully has no comment as to whether the various species encompassed by the claims are patentably distinct, and respectfully submits that Applicant need not make any such comment.

[Emphasis added.]

Applicants respectfully reiterate that the examination of Markush claims is governed by Section 803 of the Manual of Patent Examining Procedure (MPEP), which provides an exception to the normal practice of requiring restriction or election. Section 803 of the MPEP is based on the series of decisions that culminated in In re Harnisch, 206 USPQ 300 (CCPA 1980). The fact that "in many cases Markush claims do include inventions that would otherwise be considered independent and distinct" [MPEP Section 803.02; emphasis added] means that Section 803 of the MPEP provides an exception for Markush claims to the normal practice of requiring restriction or election. Applicant respectfully concludes that the subject claims are proper Markush

claims in accordance with the decision of In re Harnisch, id. and should be examined in accordance with Section 803 of the MPEP.

35 USC 112, 2nd Paragraph Rejection

Claims 24-28, 31-44 and 54-60 stand rejected under 35 USC 112, second paragraph. Applicants respectfully submit that the amendments to Claims 24 and 25 meet that rejection, and request that the Examiner review those claim amendments and withdraw the 35 USC 112, second paragraph rejection.

35 USC 112, 1st Paragraph Rejection

Claims 24-28, 31-41, 43, 44 and 54-60 stand rejected under 35 USC 112, first paragraph "because the specification, while being enabling for methods where the subject genes are MLH1 and MSH2, does not reasonably provide enablement for practicing the claimed methods with any subject genes." [Office Action, page 3.] Applicant respectfully traverses this rejection, pointing out that the amendments to Claim 24 meet this rejection.

The Office Action at page 5 states that "not all mutations result in a decreased expression of the protein" and cites to the case of p53 referencing to Passlick et al. Claim 24 has been amended such that the germline mutations detected are "selected from the group consisting of truncating-causing mutations and mutations that cause allelic loss." Mutations such as those affecting p53 as described in Passlick et al. are not

truncating - causing germline mutations nor germline mutations that cause allelic loss.

Applicant further respectfully submits that nucleic acids are nucleic acids, and proteins are proteins made up of amino acids, no matter what the gene comprising the nucleic acid is named, or the protein that is expressed from that gene is named. One of skill in the art would recognize the applicability of the subject methods to the detection of any truncating-causing germline mutation or mutation that causes allelic loss, wherein the mutation is associated with a disease or a disease-susceptibility trait.

Why should the Applicant disclose his inventive methods to the world, and then be limited to just the one or two assays that he happened to test personally? How would such restriction on the scope of an invention further the goals of the U.S. Constitution "to promote the progress of science and the useful arts by securing for limited times to . . . inventors the exclusive right to their respective . . . discoveries"? Applicant respectfully submits that the goals of the Constitution just quoted would not be served by limiting the Applicant's method to detecting mutations in the precise genes that he actually used in his experiments.

The CCPA in In re Goffe, 191 USPQ 429 at 431 (CCPA 1976) criticized the U.S. Patent and Trademark Office for attempting to limit the appellant to specific claims, lest a competitor seeking to avoid infringement could achieve this goal

readily by merely following the disclosure in the patent when it issues. The CCPA further stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work . . . . would not serve the constitutional purpose of promoting progress in the useful arts.

"[A] broad claim can be enabled by the disclosure of a single embodiment." [Precision Metal Fabricators Inc. v. Jetstream Systems Co., 6 USPQ2d 1704, 1709 (N.D. Calif. 1988).][1]

MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with

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1. See also, Rohm & Haas Co. v. Dawson Chem. Co. 217 USPQ 515 (S.D. Tex. 1983), rev'd on other grounds sub nom. Rohm & Haas Co. v. Crystal Chem Co. 722 F.2d 1556, 220 USPQ 289 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984) ("The invention . . . was a generic invention that propanil, of all of the millions of chemical compounds available, possessed useful selective, post-emergence herbicidal activity. . . . Once this invention was conceived, . . . the inventors embarked on a series of field tests in 1957 which established selectivity in post-emergence application with a number of crops. . . . Under the circumstances, Rohm & Haas was not required to limit its 1958 application to the precise crops where selectivity had at that time been demonstrated. Such a requirement would discourage an inventor from disclosing and teaching his discovery for the public's benefit until all screening had been completed, in contravention to the guiding principles underlying § 112.")

the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added.] Applicant respectfully submits that there is no reason to doubt the objective truth of statements relied upon for enabling support in the Specification for the claimed invention.

Applicant respectfully points out that at the time of filing an application, an applicant need not have any examples proving a claimed utility. An invention may be constructively reduced to practice by filing an application with no working examples at all or with paper examples. As the Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, . . . , 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991); emphasis added.]

Applicant respectfully points out that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737,

1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art."[2] [Emphasis added.]

The Patent and Trademark Office Board of Appeals and Interference [the "Board"] stated in Ex parte Forman, 230 USPQ 546 at 547 (PTO Bd. App. & Interf. 1986) that the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . . ." Further, the Board in Ex parte Mark, 12 USPQ 1904 (PTO Bd. Pat. App. & Interf. 1989) reversed an examiner's undue experimentation rejection based on the "limited successful embodiments shown and the established unpredictability associated with . . . site-specific mutageneses . . . to obtain even one biologically active mutein." The Board in reversing pointed out that

> only routine experimentation would be needed for one skilled in the art to practice the claimed invention for any given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the

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2. See also, Rengo Co. Ltd. v. Molins Mach. Co., 211 USPQ 303, 319 (3d Cir. 1980) wherein the Third Circuit stated, referring to two CCPA opinions [In re Wiggins, 179 USPQ 421, 424-425 (CCPA 1973) and In re Bode, 193 USPQ 12 (CCPA 1977)]:

> It is axiomatic that no description, however detailed, is "complete" in a rigorous sense. Every description will rely to some extent on the reader's knowledge of the terms, concepts, and depictions it embodies. Thus, an understanding of any description will involve some measure of inference. . . . [S]kill in the art can be relied upon to supplement that which is disclosed as well as to interpret what is written.

> biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

[Id. at 1907; emphasis added.]

As the Federal Circuit stated in In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165 at 1174 (U.S. ITC 1983), aff'd sub nom., Massachusetts Institute of Technology v. AB Fortia, et al., 227 USPQ 428 (Fed. Cir. 1985): "Thus, the fact that experimentation may be complex . . . does not necessarily make it undue, if the art typically engages in such experimentation."

Applicant respectfully requests that the Examiner reconsider the subject 112, first paragraph rejection in view of the amendments to Claim 24 and the above remarks, and withdraw this rejection.

35 USC 103(a)

Claims 24-28, 31-43 and 58-60 stand "rejected under 35 USC 103(a) as being unpatentable over Vogelstein et al. (WO 97/08341; published 6 March 1997." [Office Action, page 6.] Applicant respectfully traverses this rejection arguing that Vogelstein et al. does not render obvious the methods of the instant invention, and certainly does not suggest the simplicity of the Applicant's solution to the problem of allele masking.

Vogelstein et al. states at page 1 in the second full paragraph:

> Dissection of germline mutations in a sensitive and specific manner presents a continuing challenge. . . . For example, it is estimated that 20-40% of both *APC* and *hMSH2* mutations are difficult or impossible to detect with standard techniques based on PCR analysis of genomic DNA or RNA transcripts . . . . Thus there is a need in the art for a technique which is relatively simple to perform and which will detect a broad spectrum of mutations in genes of clinical interest.

[Emphasis added.] Applicant respectfully submits that the claimed methods fill the "need in the art" that Vogelstein et al. describes by providing just such "a technique which is relatively simple to perform and which will detect a broad specrum of mutations in genes of clinical interest." [*Id.*]

In contrast, the methods disclosed in Vogelstein et al. are not so "relatively simple to perform." The Vogelstein et al. methods are based on somatic cell hybridization. The non-simplicity of that technique can be detected by a glance at Figure 1 of the Vogelstein et al., which "is a schematic of the procedure for somatic cell hybrid generation." [Vogelstein et al., page 2, 3rd full ¶.]

The methods of Vogelstein et al. require fusing human

> . . . cells to rodent cell recipients to form human-rodent cell hybrids;
>
> testing said human-rodent cell hybrids to confirm the presence of said chromosome of the human in said hybrid;

> testing said hybrids which contains [*sic*] said chromosome to detect a protein product of said gene, absence of said protein product or diminished amounts of said protein product indicating the presence of a mutation in the gene of interest of the human.

[Claim 1 of Vogelstein et al., page 16.]

The only other independent claim of Vogelstein et al., Claim 19 is even more complex, reading:

> A method of detecting mutations in a gene of interest on a chromosome of a human, comprising the steps of:
>
> obtaining peripheral blood lymphocytes of the human;
>
> fusing said peripheral blood lymphocytes to rodent cell recipients to form human-rodent cell hybrids;
>
> testing said human-rodent cell hybrids to confirm the presence of said chromosome of the human in said hybrids, wherein the presence of said chromosome is tested by identifying the presence of microsatellite markers flanking the gene of interest;
>
> testing said hybrids which contains [*sic*] said chromosome to detect a protein product of said gene by Western blotting, absence of said protein product or diminished amounts of said protein product indicating the presence of a mutation in the gene of interest of the human.

Vogelstein et al. points out a problem on page 1: "In dominantly inherited diseases, mutations occur in only one allele and are often masked by the normal allele." How does Vogelstein et al. solve that masking problem? Answer: somatic cell hybridization with all its attendant complexity.

How does the Applicant solve that masking problem? Answer: simply - by using the ratio of the amount of the wild-

type protein expressed by a subject gene to the amount of wild-type protein expressed by another subject gene in said sample.

The Office Action states at page 6:

> Vogelstein fails to teach a method comprising calculating a ratio of the amount of one of the subject genes to another subject gene. However, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have calculated a ratio between one of the subject genes of Vogelstein and any other protein that one may have decided was a subject gene for the purpose of quantifying the Western blot results.

Applicant respectfully questions if calculating ratios were obvious, why did not Vogelstein et al. calculate such ratios? After all, Vogelstein et al. were searching for "a relatively simple" technique to "detect a broad spectrum of mutations in genes of clinical interest." [Vogelstein et al., page 1.]

That an invention that <u>in hindsight</u> may seem obvious because of its simplicity, is not obvious <u>before it was made</u> has been shown to be the case in many legal decisions.[3] An

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3. E.g., <u>Roberts v. Sears, Roebuck & Co</u>., 221 USPQ 504 (7th Cir. 1983), *further proceedings*, 4 USPQ2d 1527 (N.D. Ill. 1987) (not proper to deny patentability solely because of simplicity of device); <u>Globe Linings, Inc. v. City of Corvallis</u>, 194 USPQ 415, 418 (9th Cir.), *cert. denied*, 434 U.S. 985 (1977) ("An inventor will not be denied a patent simply because his invention embodies a solution which seems simple and obvious with the benefit of hindsight."); <u>Henkel Corp. v. Coral Inc</u>., 21 USPQ2d 1081, 1106 (N.D. Ill. 1990), *aff'd*, 945 F.2d 416 (Fed. Cir. 1991) (unpublished) ("the apparent simplicity of a claimed invention does not render it more easily invalidated. . . . [T]o equate simplicity with obviousness is an erroneous concept."); <u>Dolly Inc. v. Spalding & Evenflo Companies Inc</u>., 18 USPQ2d 1737, 1751 (S.D. Ohio 1991) ("The relative simplicity of a device does not render the claimed invention obvious."); <u>Creative Pioneer Products Corp. v. K Mart Corp</u>., 5 USPQ2d 1841, 1844

invention's very simplicity may be evidence of its nonobviousness. [In re Osplack, 93 USPQ 306 at 308 (CCPA 1952).]

As the Court of Claims[4] noted in Palmer v. United States, 163 USPQ 250 at 254 (Ct. Cl. 1970): "[U]nder the circumstances . . . the simplicity of plaintiff's light is a hallmark of its unobviousness." [Emphasis added.] The Second Circuit in American Safety Table Co. v. Schreiber, 122 USPQ 29, 36 (2d Cir. 1959), *cert. denied*, 361 U.S. 915 (1959) stated: "[T]he very simplicity of a new idea is the truest and most reliable indication of novelty and invention."[5]

(S.D. Tex. 1986) ("A simple invention is not necessarily an obvious one."); State Industries, Inc. v. Mor-Flo Industries, Inc., 231 USPQ 242(3), 247 (E.D. Tenn. 1986), *aff'd*, 818 F.2d 875(4) (Fed. Cir. 1987), *cert. denied*, 484 U.S. 845 (1987) ("The invention here in dispute is simple and there is an inclination to find such simple things to be obvious. However, if the invention were so obvious why hadn't anyone come up with it . . . ?").

4. In the Federal Circuit's first reported opinion, South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982), the Federal Circuit adopted as binding precedent "the holdings of our predecessor courts, the United States Court of Claims and the United States Court of Customs and Patent Appeals [CCPA]. . . ." [Emphasis added.]

5. A.E. Staley Mfg. Co. v. Harvest Brand, Inc., 171 USPQ 795, 797 (10th Cir. 1971), *cert denied*, 406 U.S. 974 (1972) ("simplicity is not a bar to invention as long as the steps taken are not obvious to the ordinary mechanic"); Ellipse Corp. v. Ford Motor Co., 171 USPQ 513, 517 (7th Cir. 1971), *cert. denied*, 406 U.S. 948 (1972) ("the fact that the solution to a problem is simple or appears so when viewed in retrospect does not mean the solution was obvious when it was conceived"); Chesapeake & Ohio Ry. Co. v. Kaltenbach, 37 USPQ 288 (4th Cir. 1938) ("because an idea, once demonstrated, seems simple, it does not follow that it only involves mechanical skill and is not an invention").

Gentry Gallery Inc. v. Berkline Corp., 41 USPQ2d 1345, 1349 (D. Mass. 1996), *aff'd in part, rev'd in part*, 45 USPQ 1498

The Court of Customs and Patent Appeals stated in In re Sporck 133 USPQ 360(2) (CCPA 1962): "[T]he simplicity of new inventions is often times the very thing that is not obvious before they are made." [Emphasis added.] The Court of Claims has also stated: "Experience has shown that some of the simplest advances have been the most nonobvious." [van Veen v. United States, 151 USPQ 506 (Ct. Cl. 1967).]

Nowhere in Vogelstein et al. is there any suggestion of using a ratio of the amounts of proteins expressed by different genes to detect a germline mutation, and a fortiori there is certainly no suggestion in Vogelstein et al. of using the ratio or ratios of the amounts of wild-type proteins expressed by one subject gene to one or more other subject genes to determine whether a mutation exists in any of the subject genes. Applicant respectfully concludes that Vogelstein et al., disclosing complex methods based on somatic cell hybridization, does not render obvious Applicant's methods.

The inventiveness of the methods of this invention are evidenced by their simplicity. [In re Osplack, supra; Palmer v. United States, supra; American Safety Table v. Schreiber, supra; In re Sporck, supra; and van Veen v. United States, supra.] Applicant respectfully requests that the Examiner reconsider the

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(Fed. Cir. 1998) ("This change, which has been extraordinarily popular, certainly seems simple. Any graduate of a high school art class could design the essentials with a piece of paper and pencil in ten minutes. But no one did.").

instant 103(a) rejection over Vogelstein et al. in light of the above remarks and case law, and withdraw this rejection.

35 USC 103(a) Claim 44

Claims 24 and 44 stand rejected under 35 USC 103(a) as being unpatentable over Vogelstein et al. (WO 97/08341) in view of Kinzler et al. (U.S. Patent 6,048,701). The Office Action at page 7 states that "Claim 44 is drawn to methods where the protein detection is automated. Vogelstein teaches as described above, but fails to teach automated immunological methods. However, automated immunological methods are well known in the art as evidenced by the teachings of Kinzler." Applicant respectfully traverses this rejection relying upon the above arguments in response to the obviousness rejection solely over Vogelstein et al. Kinzler et al. contains no disclosure concerning calculating a ratio or ratios of the amounts of wild-type protein expressed by subject genes for use in detecting germline mutations.

Claim 44 is dependent on Claim 24. As the Federal Circuit stated in In re Fine, 5 USPQ2d 1596 at 1600 (Fed. Cir. 1988): "Dependent claims are nonobvious under Section 103 if the independent claims from which they depend are nonobvious." For the reasons stated in the section above, Claim 24, the independent claim upon which Claim 44 depends, is nonobvious over Vogelstein et al. Since nothing in Kinzler et al. adds to the

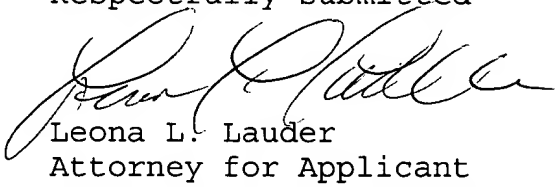
disclosure of Vogelstein et al. to render Claim 24 obvious, Claim 44 is similarly nonobvious in view of In re Fine (*id.*).

Applicant respectfully concludes that neither Vogelstein et al. nor Kinzler et al., alone or in combination, render the instantly claimed invention obvious. Applicants respectfully request that the Examiner review this rejection in view of the above remarks and case law, and withdraw this rejection.

CONCLUSION

Applicant respectfully concludes that the claims as amended are in condition for allowance, and earnestly requests that the claims be promptly allowed. If for any reason Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicant at (415) 981-2034.

Respectfully submitted



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Dated: April 2, 2002

APPENDIX 2

Claim 24 has been amended as follows:

24. (Twice amended) A method of detecting a disease or a disease susceptibility trait in an organism, wherein said disease or said disease susceptibility trait is associated with a germline mutation in one of two or more subject genes, **wherein said germline mutation is selected from the group consisting of truncating-causing mutations and mutations that cause allelic loss** comprising:

(a) isolating a ~~normal~~ biological sample from said organism;

(b) immunologically quantitating the amount of wild-type protein in said sample, that is expressed by each of the subject genes;

(c) calculating the ratio of the amount of the wild-type protein expressed by one of said subject genes in said sample, to the amount of wild-type protein expressed by the other subject gene in said sample, or to each of the amounts of wild-type protein expressed by each of the other subject genes in said sample;

(d) determining whether the ratio or ratios calculated in step (c) reflects or reflect an abnormally low level of a wild-type protein expressed by either of the subject genes, or by any of the subject genes in said sample; and

(e) concluding that if the ratio or ratios calculated in step (c) indicates or indicate that there is an abnormally low level of a wild-type protein expressed by one of the subject genes in said sample, that that subject gene contains a germline mutation in one of its alleles, and that the subject organism is affected by the disease or the disease susceptibility trait associated with said germline mutation.

Claim 25 has been amended as follows:

25. (Amended) The method of Claim 24 wherein step (d) comprises comparing the ratio or ratios calculated in step (c) to ~~the~~ **a** comparable mean or means of ratios calculated from the amounts of wild-type proteins expressed by the subject genes in comparable biological samples from organisms of the same taxonomic classification as the subject organism, ~~that~~ **wherein said organisms of the same taxonomic classification as the subject organism** are unaffected by said disease or by said disease susceptibility trait.

Claim 32 has been amended as follows:

32. (Amended) The method of Claim ~~31~~ **24** wherein said mutation is selected from the group consisting of nonsense mutations, frameshift mutations, promoter mutations, enhancer mutations, splice site mutations, null mutations, and poly-A tail mutations.